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Sponsor: Sanofi **Drug substance(s):** Fexofenadine Hydrochloride	**Study Identifiers:** U1111-1205-1504, NCT03664882 **Study code:** LPS15332
Title of the study: Phase 3, Single-Center, Sequential and Parallel-Group, Double-Blind, Randomized Study Evaluating the Efficacy and Safety of Fexofenadine Hydrochloride 180 mg (Allegra®/Telfast®) versus Placebo in Subjects Suffering from Seasonal Allergic Rhinitis with Symptoms Aggravated in Presence of Pollutants	
Study center(s): This study was conducted at 1 study center in Canada	
Study period: Date first subject enrolled: 05/Nov/2018 Date last subject completed: 03/Jan/2019	
Phase of development: Phase 3	

Objectives:

The objective of the study was to demonstrate the aggravation of the seasonal allergic rhinitis (SAR) symptoms in presence of pollutants (diesel exhaust particulate [DEP]) using an environmental exposure unit (EEU) and to evaluate the efficacy and safety of a single dose of fexofenadine hydrochloride (HCl) 180 mg film-coated tablet under conditions closer to real world using a controlled allergen challenge.

The first primary objective of the study was to demonstrate the aggravation of the SAR symptoms in presence of pollutants (DEP) using an EEU.

The second primary objective was to evaluate the efficacy of fexofenadine HCl in subjects suffering from SAR with symptoms aggravated in presence of DEP.

The secondary objective of this study was to evaluate the safety of a single dose of fexofenadine HCl 180 mg.

Methodology:

This study was a Phase 3, sequential and parallel-group with randomization ratio 1:1 in Period 3, double-blind, single center, placebo-controlled study. Five visits to the site were planned per subject.

EEU methodology

The EEU was a specifically engineered room and the setup included location of chairs, feeder, fans, and Rotorod® sampling equipment. Two custom-engineered computers and laser-aided system dispersed pollen and DEP.

The pollen and DEP were propelled via selectively placed groups of fans and adjustable floor level wall vent over the participant seating area. A particle black carbon (BC) microaethalometer was used to track DEP in exposure room.

Ragweed pollen was sourced from the USA and was independently tested for fungal and bacterial contamination by a Canadian company.

Number of subjects:

An estimation of 340 subjects to qualify during the EEU challenge in Period 1 was done; of 375 subjects screened, 266 subjects were considered eligible for the study. A total of 266 eligible subjects attended Period 1, 261 subjects attended Period 2, and 253 subjects attended Period 3. Out of the total 253 subjects in Period 3, 127 subjects were randomized to fexofenadine HCl 180 mg and 126 subjects were randomized to placebo group and all the subjects who were randomized, completed the study. A total of 257 subjects were included in the Evaluable Population, 251 subjects were analyzed for efficacy in the modified intent-to-treat (mITT) Population, and 253 subjects were analyzed for safety in the Safety Population (analysis population definitions are provided in the statistical methods section below).

Diagnosis and criteria for inclusion:

- Adult males or females between the ages of 18 and 65 suffering from SAR provoked by ragweed pollen.
- Having a 2-year history of SAR with positive skin prick test to ragweed allergen at Screening with a wheal diameter at least 3 mm larger than that produced by the negative control.
- Subjects with antecedents of allergic SAR symptoms aggravation when exposed to pollen and air pollutants (i.e., cleaning products, diesel, paints).
- Signed written informed consent.
- Subjects having a Total Nasal Symptom Score (TNSS) ≥3 at least at 1 time point during the first 3 hours in Period 1 (Visit 2) after pollen challenge test, in the EEU.

Study treatments

Investigational medicinal product (1): Fexofenadine HCl

Formulation: film coated tablets, single dose of 180 mg

Route(s) of administration: oral

Dose regimen: Single dose administration

Investigational medicinal product (2): Matching placebo

Formulation: Identical film coated tablets

Route(s) of administration: oral

Dose regimen: Single dose administration

Duration of treatment: A single dose of fexofenadine HCl 180 mg or placebo was administered

Criteria for evaluation:

Primary endpoints:

- The first primary endpoint was the area under the curve (AUC) of the TNSS from H0 to H+12 during Periods 1 and 2.
- The second primary endpoint was the AUC of the TNSS from H+2 (planned time of investigational medicinal product [IMP] administration) to H+12 during Period 3.

Secondary endpoints:

Efficacy:

- The AUC of the Total Symptom Score (TSS) from H+2 (planned time of IMP administration) to H+12.
- The AUC of individual symptom score (rhinorrhea, sneezing, nasal itching, itchy eyes, watery eyes, red or burning eyes, itching of the ears or palate or throat, and nasal congestion) from H+2 (planned time of IMP administration) to H+12.
- The TNSS, TSS, and individual symptom scores by time point.

Safety:

- Incidence and nature of adverse events (AEs).

Symptom score rating:

Subjects scored their symptoms using the below rating scale.

- 0 = None, symptom is completely absent.
- 1 = Mild, symptom is present, but not bothersome.
- 2 = Moderate, symptom is bothersome, but tolerable.
- 3 = Severe, symptom is hard to tolerate, I would like to have a treatment.

Symptoms including rhinorrhea, sneezing, nasal congestion, nasal itching, itchy eyes, watery eyes, red or burning eyes, and itching of the ears or palate or throat were evaluated.

- TNSS: It was the sum of rhinorrhea, sneezing, and nasal itching scores (maximum 9).
- TSS: It was the sum of rhinorrhea, sneezing, nasal itching, itchy eyes, watery eyes, red or burning eyes and itching of the ears or palate or throat scores (maximum 21).

Statistical methods:

Primary analysis:

The primary analysis was structured as a hierarchical procedure:

1. The first primary analysis was the comparison of the first primary endpoint between Period 1 and Period 2 at a two-sided 5% type I error rate level, using a mixed model for repeated measures (MMRM), adjusted on baseline TNSS (H0) and on pollen counts (at subject level) for each period (1 and 2) with period as fixed categorical effect, in the Evaluable Population.
2. If and only if the first primary analysis was statistically significant, the second primary analysis was planned to be conducted at the same two-sided 5% type I error rate level, in the mITT Population, using the treatment group allocated by randomization: the second primary endpoint was compared between treatment groups in Period 3, using an analysis of covariance (ANCOVA) with treatment as fixed categorical effect and TNSS at H+2 as covariate.

Furthermore, the TNSS was described respectively in the Evaluable Population by period on Periods 1 and 2, and in the mITT by treatment group on Period 3. In addition, the mean and 95% confidence interval (CI) in TNSS, TSS, and score of individual symptoms were plotted across time from H0 to H+12 overall for Periods 1 and 2.

Analysis of secondary efficacy endpoints:

All secondary efficacy endpoints were analyzed or summarized using the mITT Population in Period 3.

The secondary efficacy endpoints analyses were planned to be only descriptive if the second primary efficacy endpoint was nonsignificant, otherwise the following analyses were conducted.

All secondary efficacy endpoints based on the $AUC_{2\text{-}12}$ were analyzed using an ANCOVA with treatment as fixed categorical effect and the baseline values (ie, H+2) as covariate.

The TNSS, TSS, and score of individual symptoms versus time from H+2 to H+12 by treatment group were analyzed using an MMRM, with treatment, time point, and treatment group by time point interaction as fixed effect with their respective baseline (H+2) scores as covariate. The statistics from the MMRM (least-square [LS]-means and its 95% CI) were plotted across time for each treatment group.

A hierarchical procedure was used to control the type I error and handle multiple endpoints. If the first primary endpoint analysis was significant at the 5% alpha level, the second primary and secondary efficacy endpoints were tested sequentially, see section “Multiplicity Issues”.

In addition, the mean and 95% CI in TNSS, TSS, and score of individual symptoms were plotted across time from H0 to H+12 by treatment group for Period 3.

Analysis of safety:

Safety analysis of AEs was descriptive, based on the Safety Population. In addition, pre-treatment AEs were described by period and based on the Eligible Subjects and Evaluable Population.

Summary:

Disposition and Demography:

Overall, 375 subjects were screened, of whom 266 subjects (70.9%) were considered eligible for the study and 257 subjects were included in Evaluable Population. The most common reason for screen failure was not meeting the inclusion criteria 02 (Having a 2-year history of SAR with positive skin prick test to ragweed allergen at Screening with a wheal diameter at least 3 mm larger than that produced by the negative control). A total of 266 eligible subjects attended Period 1, 261 subjects attended Period 2, and 253 subjects attended Period 3. Five eligible subjects discontinued the study before entering Period 2 and the reasons for discontinuation were AE (2 subjects), consent withdrawal (1 subject), poor compliance to protocol (1 subject), and exclusion criteria 22 (1 subject). Eight eligible subjects discontinued the study before entering Period 3 and the reasons for discontinuation were schedule conflict (4 subjects), AE (2 subjects), exclusion criteria 9 (1 subject), and EEU challenge intolerance (1 subject).

Out of the total 253 subjects in Period 3, 127 subjects were randomized to fexofenadine HCl 180 mg and 126 subjects were randomized to placebo group. All the subjects who were randomized, completed the study.

The fexofenadine HCl and placebo groups were similar in the demographic and baseline characteristics (alcohol/smoking habits) with more females than males (61.1% and 70.4% of females in fexofenadine HCl and placebo group, respectively). The mean age was approximately 40 years (40.0 and 41.5 years old in fexofenadine HCl and placebo group, respectively).

Results:

All endpoints measured by AUC were log-transformed hence model assumptions for MMRM and ANCOVA were met.

SAR symptoms aggravation in presence of DEP:

First primary endpoint: The AUC_{0-12} for TNSS was higher in Period 2 (pollen + DEP) compared to Period 1 (pollen alone), with a mean AUC_{0-12} of 41.22 versus 36.25 respectively. The LS-mean difference (95% CI) between periods (Period 2 - Period 1) calculated using MMRM model for Log AUC_{0-12} of TNSS was 0.13 (0.081 to 0.182), which was statistically significant ($p<0.0001$) showing higher TNSS in Period 2 compared to Period 1, indicating aggravation of SAR symptoms in presence of pollutants. The TNSS values were consistently higher across all timepoints in Period 2 compared to Period 1.

Efficacy of the fexofenadine HCl 180 mg versus placebo:

Second primary endpoint: The AUC_{2-12} for TNSS in Period 3 was lower in fexofenadine HCl group compared to placebo, with a mean AUC_{2-12} of 18.53 versus 26.34, respectively. The LS-mean difference (95% CI) between treatment groups (fexofenadine HCl – placebo groups) calculated using ANCOVA for Log AUC_{2-12} of TNSS was -0.24 (-0.425 to -0.047), which was statistically significant ($p=0.0148$) indicating lower TNSS, adjusted on baseline (H+2), in fexofenadine HCl group compared to placebo. The TNSS values were consistently lower across all timepoints after treatment administration in fexofenadine HCl group compared to placebo.

Secondary endpoints:

The AUC_{2-12} for TSS in Period 3 was lower in fexofenadine HCl group compared to placebo, with a mean AUC_{2-12} of 35.16 versus 47.96, respectively. The LS-mean difference (95% CI) between treatment groups (fexofenadine HCl – placebo groups) calculated using ANCOVA for Log AUC_{2-12} of TSS was -0.18 (-0.369 to 0.015; $p=0.0711$) indicating lower TSS in fexofenadine HCl group compared to placebo. As the p-value was not statistically significant at 5% level based on the hierarchical procedure used to handle multiple endpoints, the other secondary endpoints were considered descriptive and not deemed statistically significant.

The mean AUC_{2-12} for individual symptom scores (rhinorrhea, sneezing, nasal itching, itchy eyes, watery eyes, red or burning eyes, itching of the ears or palate or throat, and nasal congestion) was lower in fexofenadine HCl group compared to placebo.

The mean TNSS at H+2.5 and at all later timepoints in Period 3 was lower in fexofenadine HCl group compared to placebo with the LS-mean difference (calculated using MMRM) between treatment groups (fexofenadine HCl – placebo groups) ranging from -0.4 to -0.8.

The mean TSS at H+2.5 and at all later timepoints in Period 3 was lower in fexofenadine HCl group compared to placebo with the LS-mean difference (calculated using MMRM) between treatment groups (fexofenadine HCl – placebo groups) ranging from -0.6 to -1.4.

The mean individual symptom scores at H+2.5 and at all later timepoints in Period 3 were lower (or equal) in fexofenadine HCl group compared to placebo.

Safety Results:

No deaths or adverse events of special interest (AESIs) were reported in this study.

Extent of Exposure:

All subjects received the study treatment as instructed, after 120 minutes from start of pollen + DEP challenge (Period 3) with treatment compliance of 100% in both treatment groups.

A total of 266 eligible subjects entered the EEU challenge in Period 1 (pollen only), 261 subjects in Period 2 (pollen + DEP), and 253 subjects in Period 3 (pollen + DEP + IMP) of the study. Five subjects discontinued the study before entering Period 2 and 8 subjects discontinued the study before entering Period 3. Only 1 subject of 261 (0.4%) withdrew in Period 2 after 61 minutes of exposure to pollen and DEP, due to intolerable symptoms of chest discomfort and dyspnea.

Exposures to ragweed pollen and DEP were comparable between study periods.

Pretreatment AEs:

One subject experienced a pretreatment serious adverse event (SAE) of cellulitis streptococcal of severe intensity which led to discontinuation from the study. This SAE occurred after the Screening visit (Visit 1) and before the first EEU exposure (Visit 2) of Period 1.

A total of 5 subjects experienced pretreatment nonserious AEs that led to discontinuation from the study. One subject discontinued study due to intolerable symptoms of chest discomfort and dyspnea during EEU challenge in Period 2 and these symptoms were reported as pretreatment AEs; however, the reason for discontinuation was specified as EEU challenge intolerance by the Investigator.

A total of 121/266 (45.5%) eligible subjects experienced at least 1 pretreatment AE.

The most frequently reported primary system organ class (SOCs) were nervous system disorders (14.7%, 39/266 subjects) and infections/infestations (14.7%, 39/266 subjects).

The most frequently reported pretreatment AEs were headache (12.4%, 33/266 subjects) and upper respiratory tract infection (9.8%, 26/266 subjects).

Treatment-emergent adverse events (TEAE):

No subjects experienced a treatment-emergent SAE, AESI, or TEAE that led to discontinuation from the study.

The proportion of subjects with at least 1 TEAE during the study was comparable between the 2 treatment groups: 16/127 subjects (12.6%) in fexofenadine HCl group versus 19/126 subjects (15.1%) in the placebo group.

One subject (0.8%, 1/127 subjects) from fexofenadine HCl group experienced a TEAE (dry mouth) that was considered related to the IMP.

The most frequently reported primary SOCs (fexofenadine HCl group versus placebo group) were immune system disorders (4.7%, 6/127 subjects versus 5.6%, 7/126 subjects) and respiratory, thoracic and mediastinal disorders (1.6%, 2/127 subjects versus 4.0%, 5/126 subjects).

Issue date: 26-Dec-2019